## REMARKS

Entry of the foregoing and favorable reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow are respectfully requested.

By the present amendment Claims 17 and 25 have been cancelled solely to expedite the prosecution of the present application and not to acquiesce to the Examiner's rejection. Applicants reserve their right to file a divisional or continuation application directed to the cancelled subject matter.

Claims 15, 16, 18, 23, 24 and 26 have been amended solely to clarify the present invention. The support for these amendments can be found throughout the specification, including at page 14, line 3 to line 26. Claims 27 to 32 have been added. Support for the newly presented claims can be found throughout the specification, including at page 14, line 3 to line 26. Support for Claim 28 appears at least on page 13 of the application as filed.

## Vector Design

Prior to specifically addressing the rejections brought to bear by the Examiner, Applicants would like to briefly clarify the vector design used in the claimed method. It was well known in the art at the time of filling of the present application that the adenoviral genome comprises early transcription units, known as E1A, E1B, E2, E3 and E4 and one late unit (major late) which is controlled by the MLP (major late promoter) that produces five families (L1-L5) of late mRNAs which give after translation all of the major capsid proteins. The schematic representation of the human adenovirus genome is set forth below:

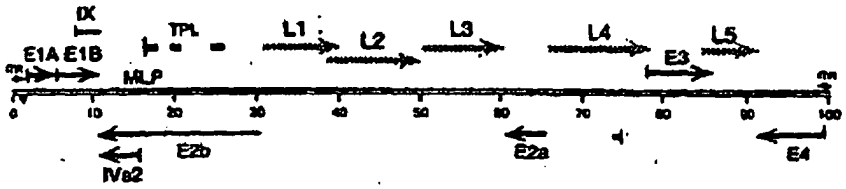


**Figure 1** Schematic representation of the human adenovirus genome. Black arrows depict immediate-early, early, and delayed-early genes and hatched arrows depict the late genes. The inverted terminal repeats are labeled ITR and the packaging sequence is denoted as ψ. MLP corresponds to the major late promoter.

As can be seen from the above schematic representation, the "native" MLP overlaps the E2 transcription unit.

The vector of the present invention lacks the E1A, E1B and E3 regions thus making it replication defective. It further comprises a cytokine expression cassette wherein the cytokine gene is placed under the control of a promoter present in the adenoviral vector (i.e., an adenoviral promoter) or a promoter which is exogenous to the adenovirus (i.e., a non-adenoviral promoter). The present application illustrates an E1A, E1B and E3 deleted adenoviral vector comprising a cytokine gene in the E1 region under the control of an adenoviral MLP promoter. Therefore, the adenoviral promoter which is used to control the expression of the cytokine gene in the E1 region is an **additional** MLP promoter (Ad2 MLP) located upstream of the cytokine gene in the E1 region. Since both E2 and E4 regions are still present in the viral backbone, the native MLP promoter which overlaps the E2 region is maintained in the viral backbone to ensure the production of the late viral products (L1-L5) and thus the viral infectivity. Thus, the present invention does not contemplate the replacement of the native MLP which is essential in production of viral capsid proteins.

**35 U.S.C. § 112, First Paragraph**

Turning now to the Official Action, Claims 15 to 18 and Claims 23 to 26 have been rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art, at the time the application was filed, that the inventors had possession of the claimed invention.

In rendering this rejection, the Examiner purports that the phrase "promoter present in said replication-defective adenoviral vector or an exogenous promoter" does not have support in the specification as originally filed.

Claim 15 has been amended to recite that the cytokine is under the control of an adenovirus late promoter. Claim 23 depends on claim 18, which depends on new Claim 27. New Claim 27 recites that the adenovirus late promoter is replaced by a promoter which is exogenous to the adenovirus or is the early E1A promoter. These amendments are supported at page 14, line 3 to line 26 of the specification. This amendment should now obviate-in-part this rejection.

Furthermore, the Examiner purports that Claims 15, 25 and 26 contain new matter. Claim 25 has been deleted, as far as this rejection pertains to claims 15 and 26, Applicants offer the following remarks.

It is well settled in the early case law that an amendment introduces new matter when the matter is "not disclosed nor **suggested**" in the original application. See, *Mackey Radio & Tel. Co. v. Radio Corp.*, 306 U.S. 86, 37 USPQ 471 (1939).

Applicants submit that the specification does in fact suggest to one skilled in the art that cytokines other than IL-2, such as gamma interferon and GM-CSF can be used in the adenoviral construct of the present invention and still maintain the same level of tumor regression. The fact that there is only one explicit example should not deny the Applicants of the other cytokines genes fully described in the specification, since there is no *haec verba* requirement in U.S. patent law that newly added claim limitations must be supported only by express disclosure; i.e., inherent and implicit disclosure are also to be considered as set forth in the MPEP §2163B. Applicants submit that there is implicit and inherent disclosure of the expression of gamma interferon and GM-CSF conveyed to those people skilled in the art.

Indeed, in a new matter rejection new and substantive information is added, which would be more properly be presented in a new application. See, Wayne-Gossard Corp. v. Sondra, Inc., 434 F. Supp 1340, 1355, 195 USPQ 777, 790 (E.d. Pa 1977) aff'd 579 F.2d 41, 200 USPQ 11 (3D Cir. 1979). However, no substantive information is being added. The application already discloses that γ-IFN and GM-CSF can be used in the adenoviral vector construct to treat tumors.

Therefore, Applicants submit that the new matter rejection cannot be maintained, since there is no legal basis that a patent specification has to describe and exemplify word for word the embodiments of each and every claim. Rather the implicit and inherent disclosure in the specification that the Examiner has not considered, which is legally incorrect.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

## 35 U.S.C. § 112, First Paragraph

## Written Description

Claims 15 to 18 and Claims 23 to 26 have been rejected under 35 U.S.C. §112, first paragraph as lacking written description. For the following reasons, this rejection is respectfully traversed. Claim 25 has been cancelled rendering this rejection of this claim moot. Applicants will discuss the rejection insofar as it applies to the other claims.

In rendering this rejection the Examiner deems that the specification does not provide a written description for replication defective adenoviruses encoding IL-2, GM-CSF or IFN-γ operably linked to an adenoviral or exogenous promoter to treat a tumor in a patient.

Applicants respectfully submit that there is an inconsistency between the Examiners statement on page 4 of the Office Action which, we quote:

> "An adequate written description of such adenoviruses requires more than a mere statement that it is part of the invention and reference to a potential method for making it; what is required is a description of the promoters and a description of how to make the adenovirus"

and on page 5, where the Examiner states

> "the rejection is not based on how to make the host of vectors encompassed by the claims."

Applicants are not only confused by this inconsistency, but also puzzled by the fact that the Examiner has not considered the legal aspect of the written description requirement. Indeed, the U.S. law requires that based on the knowledge and level of those skilled in the art at the time of filing of the application the skilled artisan would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure in the application as filed.

In evaluating an application for written description and to establish a *prima facie* case of lack of written description **the Examiner must present evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims.** See, MPEP §2163 Part II.A. The Examiner has failed to meet this initial burden!

The mere repetitious sentence throughout page 5 of the Official Action that "Adenoviral vectors encoding IL-2 or γ-INF operably linked to the promoter present in the adenovirus or an exogenous promoter that are capable of treating tumors were not well-established" is not sufficient evidence or reasoning. Rather this statement is merely a general allegation.

Furthermore, the Examiner failed to consider the level of those skilled in the art at the time of filing of the present invention. This is evidenced by the fact that the Examiner makes the statement at page 4 of the Official Action "that the description of the promoters and a description of how to make the adenovirus is required" to meet the written description requirement. When Applicants pointed out that the specification does indeed exemplify how to make the adenoviral construct, the Examiner response was the Applicants response was "off point."

The Examiner has ignored the law on this point. Indeed, in *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1384, 231 USPQ at p4 the court held that "What is conventional to one of ordinary skill in the art need not be disclosed in detail" in a patent specification. Applicants

submit that promoters, adenoviral constructs, and the cytokines cited in the specification were common general knowledge. Therefore, there is no reason why the Applicants have to repeat what is known.

The Examiner has failed to consider the above requirements that are set forth in the MPEP §2163. Nor has the Examiner provided an adequate rebuttal argument to Applicants last response which requested the Examiner to provide that which is required by law to maintain this rejection.

Indeed, the statement appearing in the Official Action on page 4 that "Procedures for administering adenoviral vectors encoding cytokines operably linked to a promoter present in the adenovirus or an exogenous promoter capable of treating tumors were not well-established," means that the Examiner has not even considered what is recited in the claims. To refresh the Examiners memory, the claims recite that the vectors **are injected** into one or more tumors. So this statement is simply irrelevant.

The statement that "The mere suggestion of replacing the adenoviral late promoter with the CMV, RSV or E1A promoter (pg. 14) is not adequate guidance for one of skill in the art to use the vector to treat tumors as claimed." Adequate guidance is not a criteria to be evaluated in a vacuum, but must be evaluated in view of what the skilled person knew at the time of filing of the application.

Moreover, Applicants submit that the Examiner has not provided any evidence or reasoning on why the skilled artisan would not have known that the Applicants had possession of the claimed invention. General allegations are insufficient. Without sufficient evidence or reasoning, Applicants deem that this rejection cannot be maintained.

Therefore, withdrawal of this rejection is respectfully requested.

## 35 U.S.C. § 112, First Paragraph

## Enablement

Claims 15 to 18 and Claims 23 to 26 have been rejected under 35 U.S.C. §112, first paragraph as being unenabled. Applicants have cancelled claim 25 rendering the rejection of the claim moot. For the following reasons, this rejection is respectfully traversed.

In rendering this rejection, the Examiner asserts that the combination of promoter, cytokine-encoding DNA and route of administration required to obtain a therapeutic effect against a tumor using adenoviral gene therapy *in vivo* was unpredictable at the time the

specification was filed. In particular, the Examiner quotes a number of articles reviewing gene therapy. In particular the Examiner discusses that targeting and long-term expression of the therapeutic gene in the affected cells has not been achieved in the art.

More specifically the Examiner states the following applicable to each reference:

(1) Miller et al "targeting strategies outlined in this review, which are currently only at experimental level will have to be translated into components of safe and highly efficient delivery systems."

(2) Deonarian indicates that "one of the biggest problems hampering successful gene therapy continues to be the ability to target a gene to a significant population of cells and express it adequately for a long period of time."

(3) Verma indicated that a "resolution to vector targeting has not been attained in the art."

(4) Crystal indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and the enable the transferred gene to be regulated."

Applicants submit the following with respect to the articles cited by the Examiner in his reliance on the unpredictability:

(1) Miller teach the targeting of gene vectors using methods such as liposome vectors, molecular conjugate vectors, transcriptional targeting, targeting proliferating cells and the exploitation of targeting using natural viral tropisms. None of these methods are described in the present invention. Therefore Miller et al is irrelevant.

(2) Deonarian disclose various ligand-targeted receptor mediated vectors for gene delivery. None of the methods disclosed therein are described in the present specification. Hence Deonarian is irrelevant.

(3) Verma discusses various vectors used to treat chronic diseases such as cystic fibrosis and ADA deficiency. This reference teaches, in the Abstract, that thanks to better delivery systems, there is hope that the techniques will succeed. Therefore, this reference does not teach unpredictability. Indeed, among the different targeting methods mentioned in Verma are use of antibody fragments, ligand to cell-specific receptors, and chemical modifications. The method

described in the present invention is not described in Verma. Therefore, this reference is irrelevant.

(4) Although Crystal states that there is a need to increase efficiency of gene transfer and increase target specificity, the present invention overcomes these problems by direct injection of the adenoviral vectors in the tumors. Therefore, Crystal is also irrelevant with respect to unpredictability.

Thus, in summary all of the references quoted by the Examiner relate to targeting problems and the long-term correction of chronic diseases by gene therapy. In marked contrast, the claimed invention overcomes the problems cited by the Examiner by direct injection into the tumors of the cytokine encoding defective adenoviral vector to provide tumor regression. Therefore, the mode of delivery solves the targeting problems contemplated in the art. Furthermore, long-term expression of the cytokine is not necessary, as it is in trying to permanently correct a genetic defect. A transient expression for a sufficient period of time is sufficient to stimulate the host's immune system thus achieving tumor regression.

At page 8 of the Official Action, the Examiner maintains that the specification does not teach administering the viral vector at a remote site. The claims were amended previously in the last Official Action to recite that the adenoviral vector is injected into one or more tumors.

At page 9, of the Official Action, the Examiner deems that due to the unpredictability in the art, that the heterologous promoters which were described in the specification would not have the same therapeutic effect. Applicants respectfully disagree with the Examiner for the following reasons.

Applicants are enclosing in Annex 1 two recent press releases illustrating that E1 and E3 deleted adenoviral vectors comprising a gene encoding either IL-2 or γIFN driven by a CMV promoter have successfully completed phase I trials and will move forward in a phase I/II program. These documents show positive results in terms of efficient gene transfer and cytokine expression. Tolerance was excellent up to the highest doses. More importantly, although phase I studies are not devoted to therapeutic benefit, promising clinical responses (tumor regression and stabilization) were observed. For example, partial and complete response (local and distal tumor regressions) were observed in 50% of cutaneous lymphomas treated with the Ad-γIFN vector. Thus, the CMV promoter works in a similar matter as the late adenoviral promoter set forth in the specification to reduce tumor regression.

Applicants therefore submit that if the CMV promoter achieves sufficient tumor expression other exogenous promoters, such as the RSV LTR and the MMTV promoter will also have the same effect, since all of these promoters are known in the art as being strong promoters.

Moreover, the Examiner deems that use of the cytokine GM-CSF in the present invention is not enabled since there is no teaching in the specification of the amounts injected into the tumor to obtain tumor regression. At least page 11 of the specification discloses that about 1 to 2 μg of interleukin was produced for $10^6$ cells. It would not be undue experimentation for the skilled artisan to obtain the same dose of GM-CSF.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

**35 U.S.C. § 112, Second Paragraph**

Claims 15 to 18 and claims 23 to 26 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite. This rejection has been obviated in part by amendment and is being traversed in part.

Claims 15, 24 and 26 have been amended such that antecedent basis for the adenovirus now appears in the claims. In claims 15 and 26 "leads" has been modified to "causes." Claims 15 and 24 to 26 have also been amended to recite that "patients" are being treating with the method to be consistent with the fact that tumor regression appears in 40-50% of patients. Furthermore, Claims 15, 18 and 24 to 26 have been amended to state that the promoter is exogenous to said adenovirus. Support for these amendments are found throughout the specification, including at page 14, line 3 to line 24. Therefore, these amendments should obviate these specific rejections.

As far as the rejection concerning the phrase "promoter present in said replication-defective adenoviral vector" is concerned, Applicants submit that this phrase is perfectly clear in view of the description. More specifically, the claimed method provides that the therapeutic vector lacks the E1a, E1B and E3 regions and comprises a cytokine under the control of one of the recited promoters. The Example and Figure 1 teach the skilled artisan how to make the construct. A shuttle plasmid is first constructed comprising the cytokine gene placed under the control of the promoter and flanked in both sides by adenoviral insertion sequences flanking the 5' the adenoviral ITR and in 3' the pIX sequence. The fragment is then introduced in 293 cells together with the linearized adenoviral genome deleted in the E3 region to produce by

homologous recombination a replication-defective adenoviral vector having the cytokine cassette inserted in replacement of the E1 region which was previously deleted.

Therefore, the Examiners contention that it cannot be determined if the E1A, E1B and E3 regions are deleted or not is unfounded. The specification clearly illustrates that the regions are deleted.

With respect to Claim 16, Applicants submit that this claim now depends from Claim 27, which should render this rejection now moot.

In view of the above, withdrawal of this rejection is respectfully requested.

**Request for Interview**

Applicants request an interview with the Examiner and his supervisor. Upon receipt of these papers, Applicants request that the Examiner contact Applicants' representative to schedule an interview.

**Summary**

From the foregoing further and favorable action in the form of a Notice of Allowance is respectfully requested and earnestly solicited.

Respectfully submitted,

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